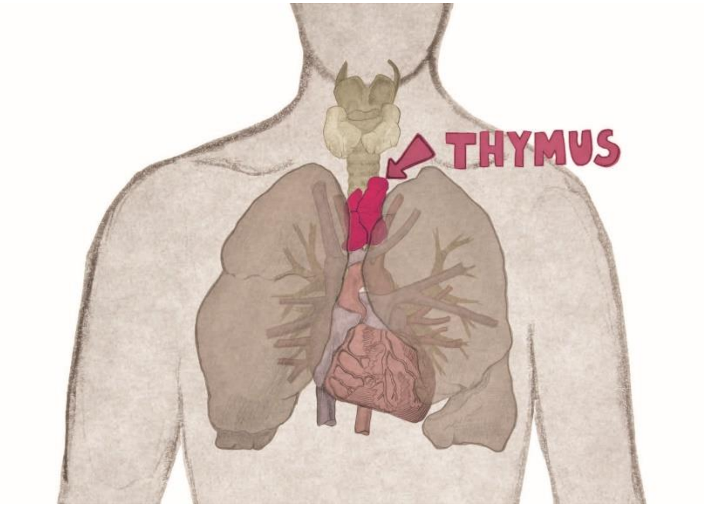
T cell Development

Double negative cells

- T cells are **born in bone marrow**.
- **Immature thymocytes** begin life in **thymus** as **emigrants** from the bone marrow.
- When they arrive in the thymus these precursors **do not express CD4**, **CD8** or **T cell receptor (TCR).**



- **CD4** and **CD8** are very useful markers in thymocyte development and, since these cells express neither, these early or immature thymocytes are said to be **"double negative"** cells.

Selection stages of T cells

During their development these **“double negative”** cells **undergo different types** of selection during the process of **maturation:**

1.Rearrangement of the T cell receptor β chain.

2. Expression of accessory molecules

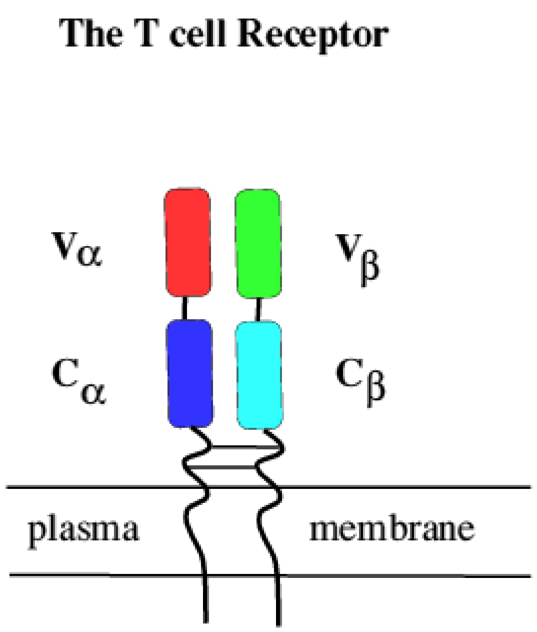
3. Rearrangement of the TCR α locus and expression of CD4+CD8+ (formation of "double positive “ thymocytes)

5. Further selection of double positive thymocytes by:

a. Negative selection and **b. Positive selection**

1. Rearrangement of T cell receptor β chain

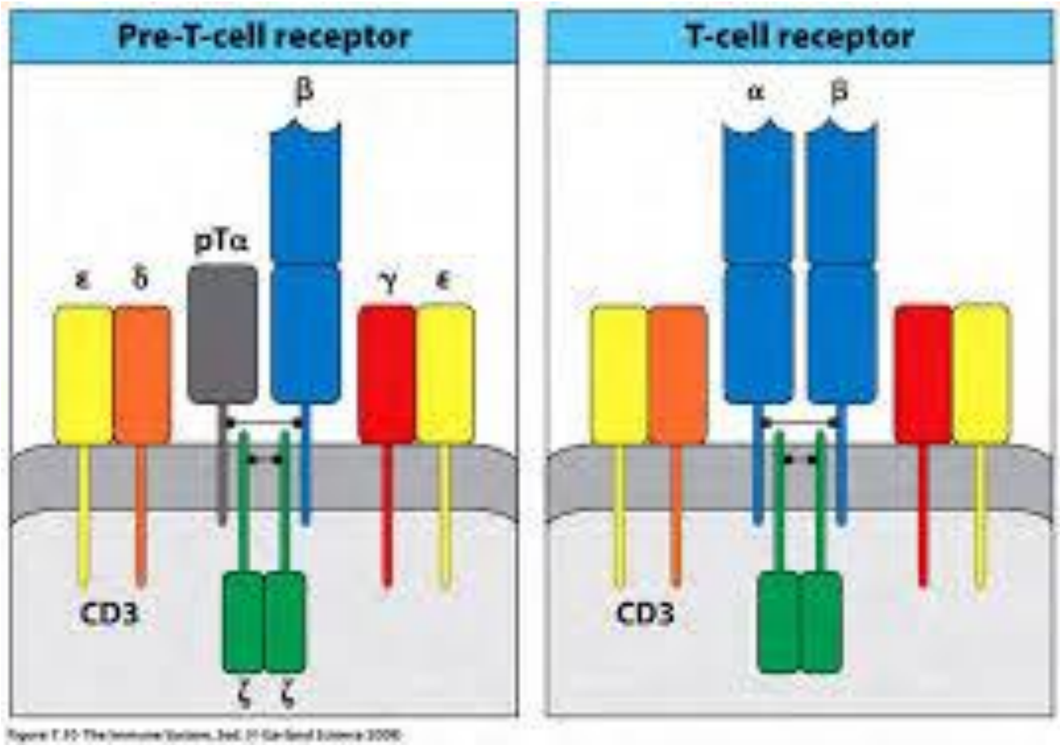
The **first critical stage** in T cell development is the **rearrangement of the T cell receptor β chain.**



- This stage is **analogous** to the rearrangement of the Ig heavy chain locus, i.e., rearrangement of multiple gene segments
- The cell needs to make a **functional rearranged TCR β chain** to avoid death by apoptosis and to be given the signal to continue its development.
- Once a **functional TCR β chain** is made, **β chain rearrangement** is switched off.

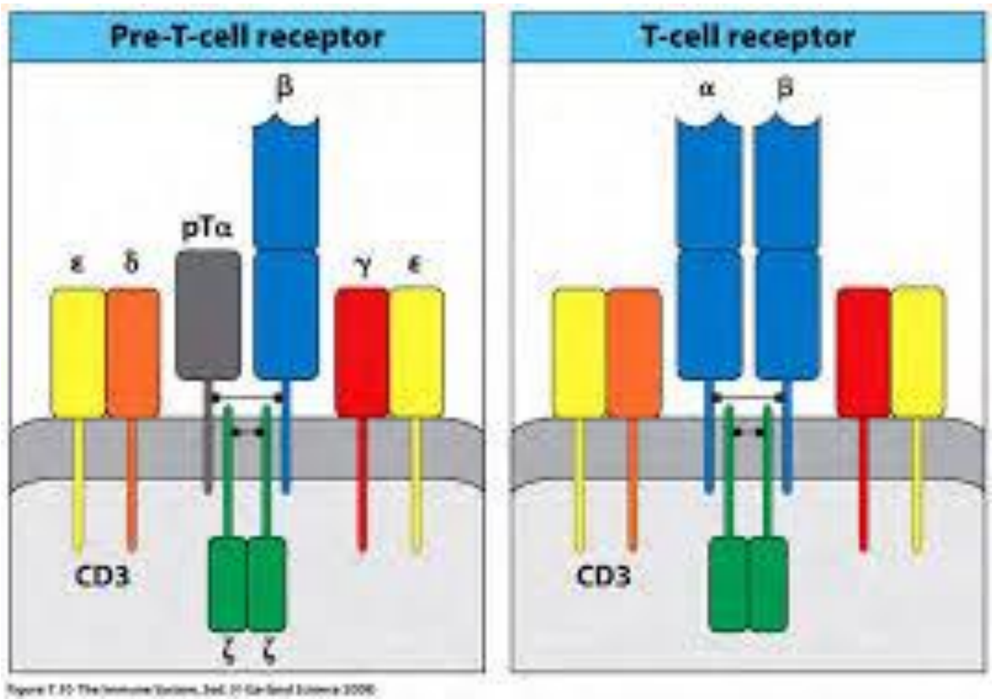
2. Expression of accessory molecules

When a T cell senses formation of a **functional TCR β chain** it expresses **molecules which can pair** with the rearranged chain to form a **pre-T cell receptor complex.** These include **one delta, one gamma, 2 epsilon** and **2 zeta chains**.

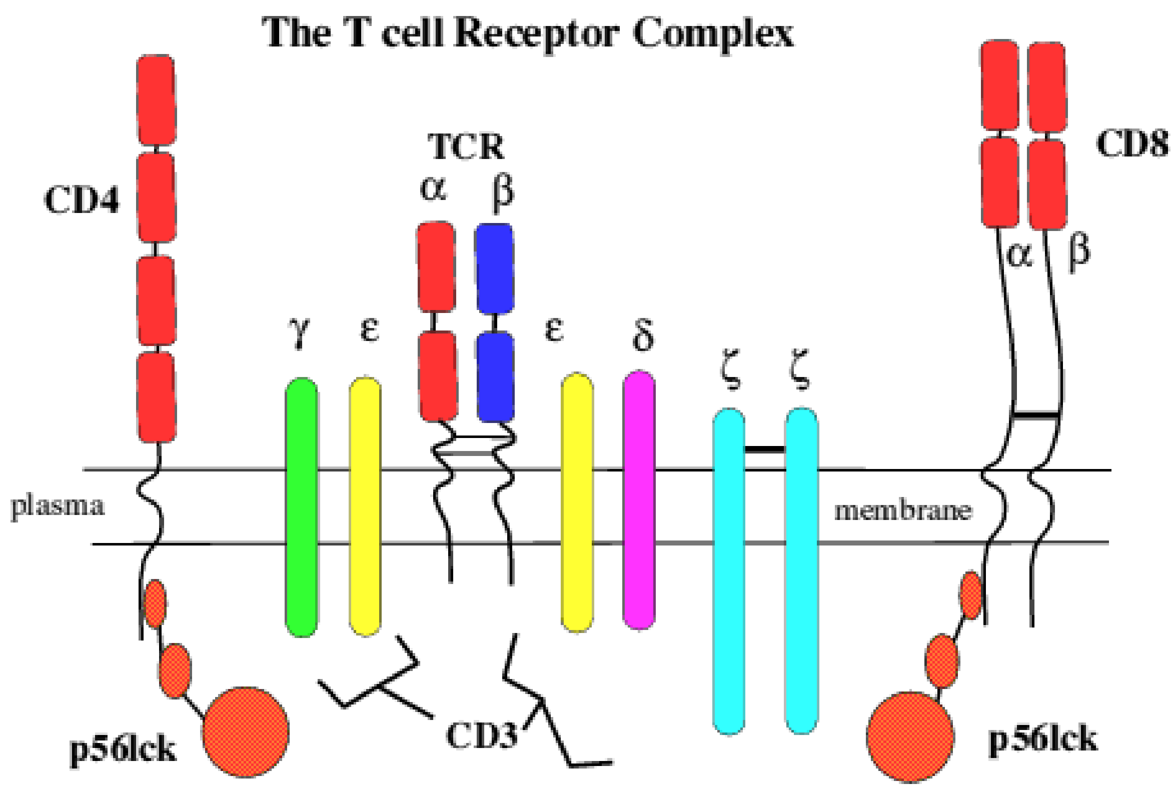


3. Rearrangement of the TCR α locus and expression of CD4+CD8+ (formation of "double positive " cells)

It is followed by rearrangement of the **TCR α locus** and expression of both the **CD4** and **CD8** molecules to form a functional T cell receptor.



Thus the **first selective step** in T cell development selects for a functional TCR β rearrangement and cells which successfully pass this scrutiny become **CD4+CD8+ "double positive " cells.**



4. Further selection in double positive thymocytes

These **double positive thymocytes** undergo **two more selective steps:**

a. Negative selection

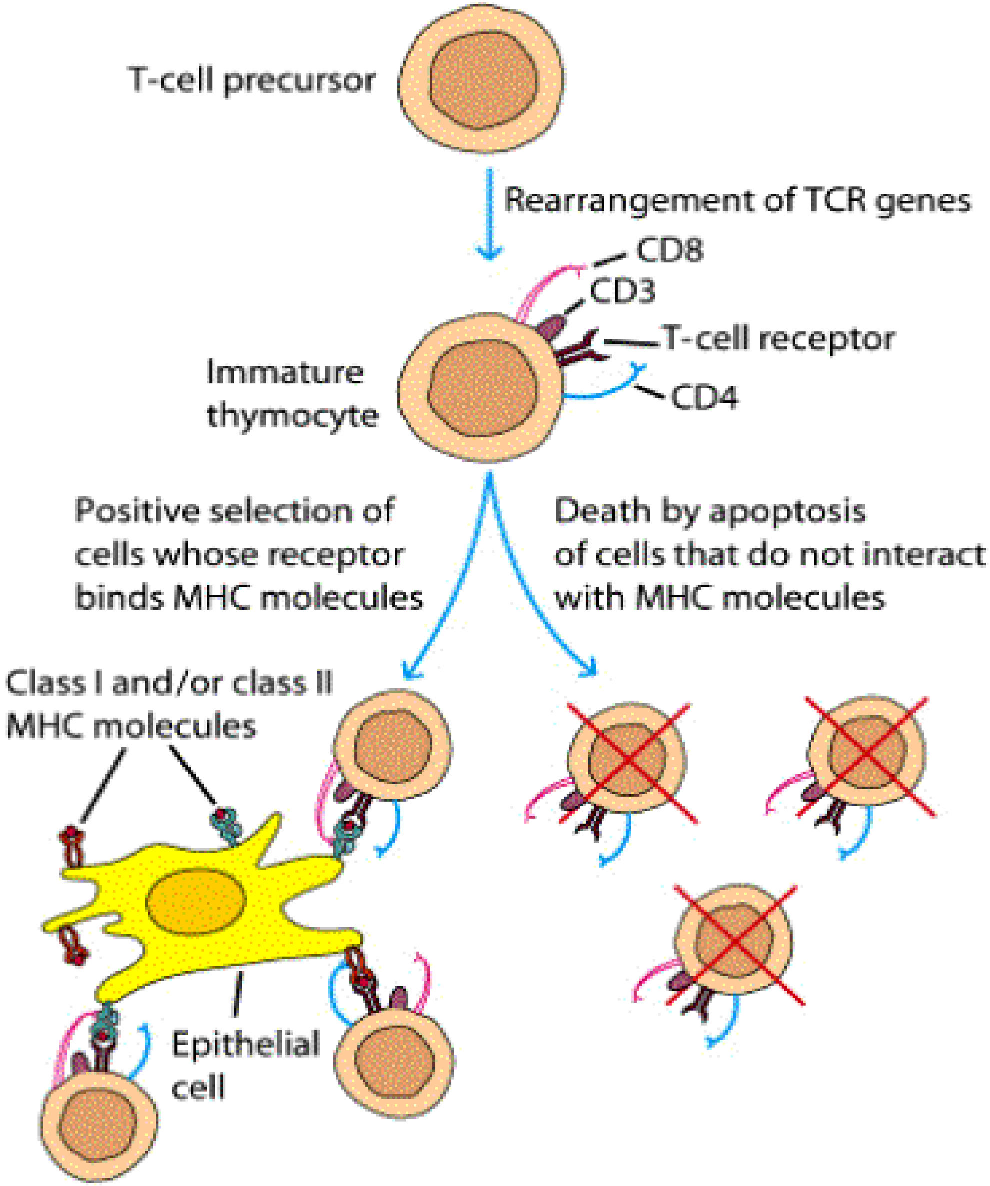
b. Positive Selection

a. Negative selection

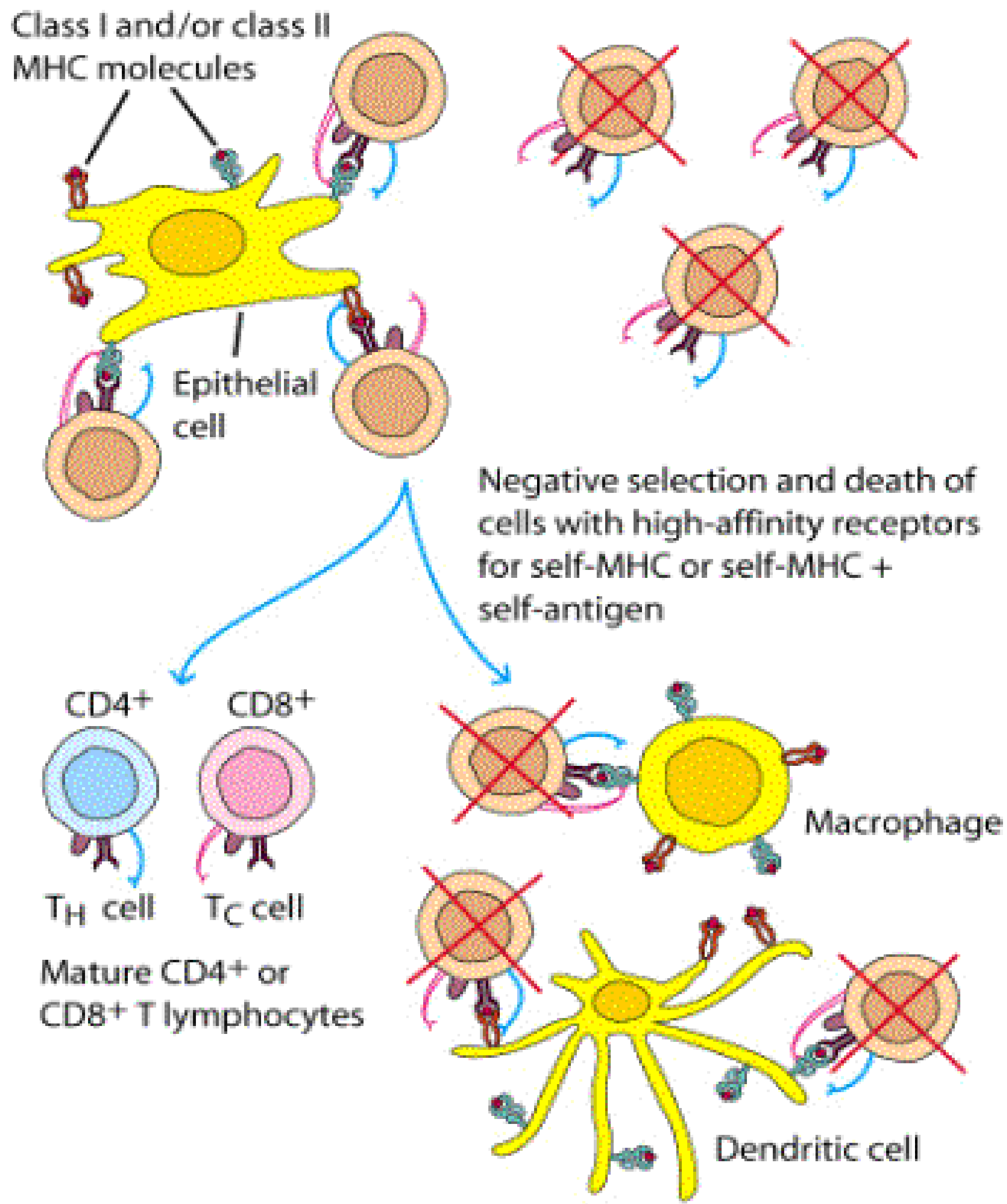
- In **first** step T cells **unable** to recognize self MHC are removed by **apoptosis** i.e. induced to undergo programmed cell death.
- In **second** step clones bearing TCR which have a **"high" affinity** for self-MHC- antigen are also deleted by apoptosis.

b. Positive Selection

- It permits survival of T cells whose TCR can recognize self-MHC- antigen with **medium affinity** .



T-cell precursor
Rearrangement of TCR genes
CD8
CD3
T-cell receptor
CD4
Immature thymocyte
Positive selection of cells whose receptor binds MHC molecules
Death by apoptosis of cells that do not interact with MHC molecules
Class I and/or class II MHC molecules
Epithelial cell


Class I and/or class II
MHC molecules
Epithelial
cell
Negative selection and death of
cells with high-affinity receptors
for self-MHC or self-MHC +
self-antigen
CD4+
CD8+
TH cell
TC cell
Mature CD4+ or
CD8+ T lymphocytes
Macrophage
Dendritic cell

Formation of CD4+ cells and CD8+ cells

- Next step is **differentiation** of **CD4+ CD8+ double positive cells** into **either** CD4+ cells or CD8+ cells.

- It is **not yet clear** how this happens and what are the factors which control and direct this differentiation.

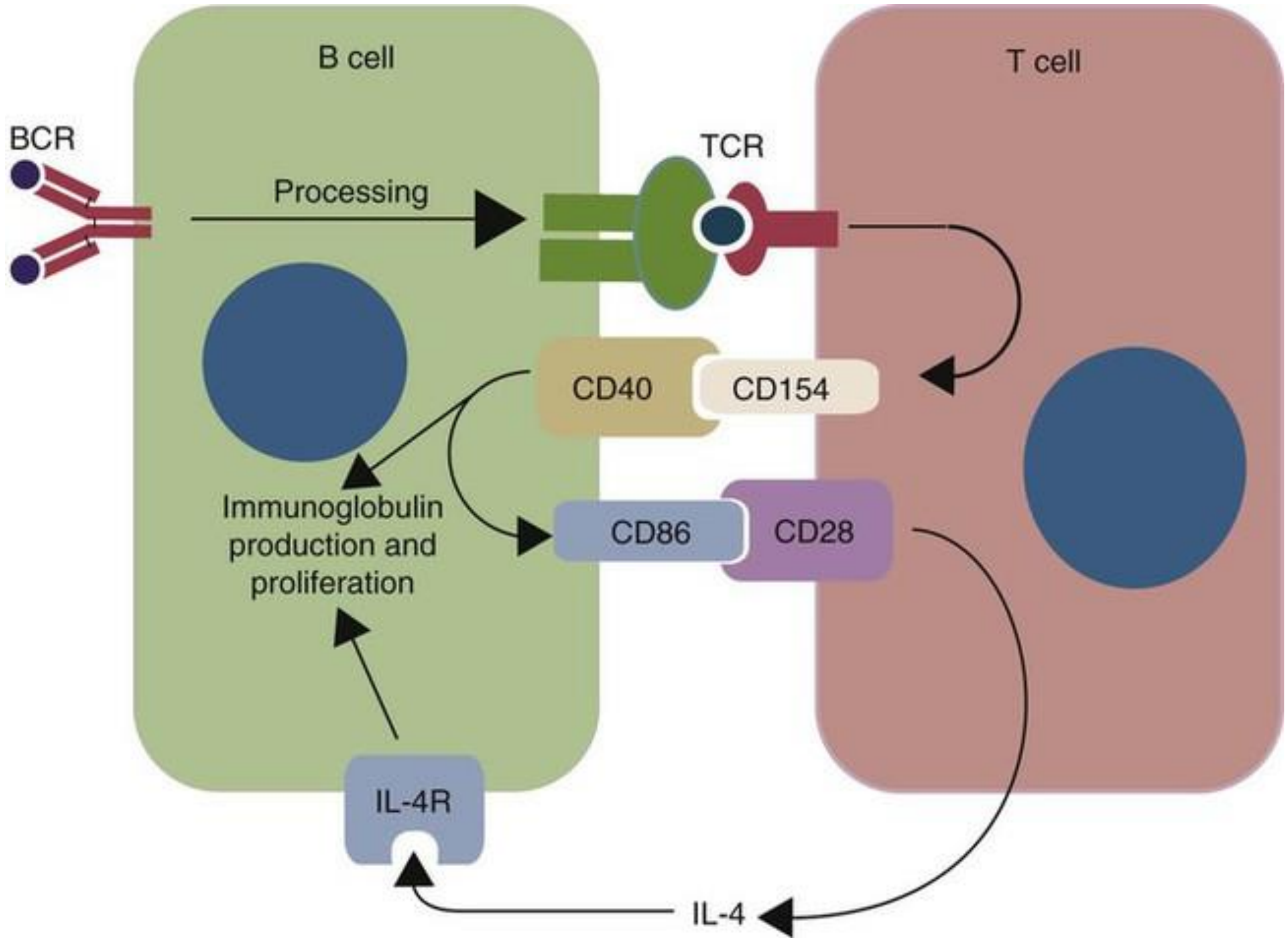
Co-stimulation

- **TCR receptor binding** is not sufficient to activate T cells.

- There is a critical role for two distinct **co-stimulator molecules** on T cells which interact with specific ligands on the surface of antigen presenting cells (APC).

- The **CD28** molecule on T cells delivers a costimulatory signal upon engaging either of its ligands, **CD80 or CD86** on APC**.**

- Another signal is provided by the **CD40L (CD 154)** molecule on the T cell when it is ligated to **CD40** on APC**.**


B cell
T cell
BCR
TCR
Processing
CD40
CD154
CD86
CD28
Immunoglobulin production and proliferation
IL-4R
IL-4

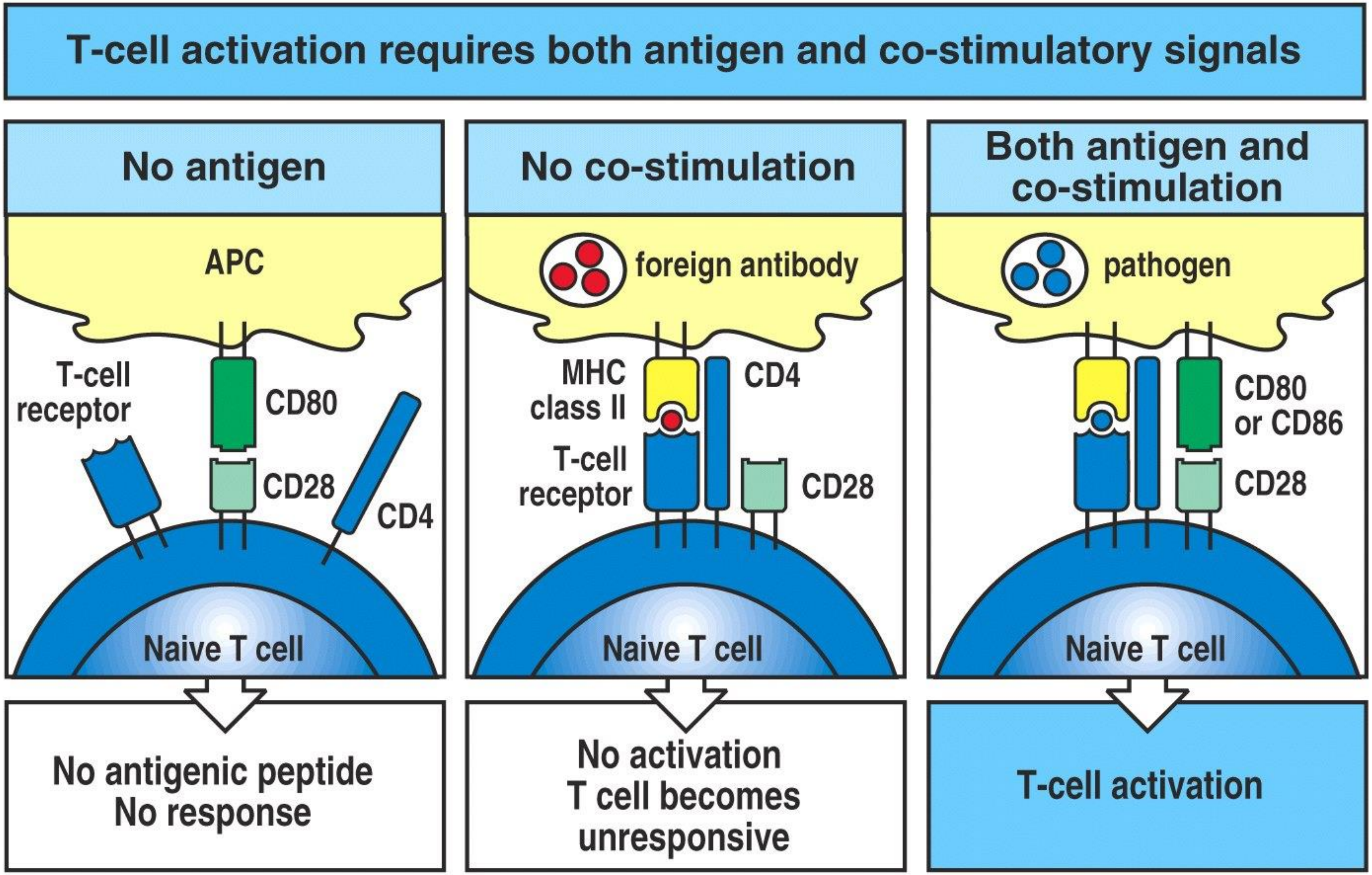


Figure 2-17 Immunobiology, 6/e. (© Garland Science 2005)

- The expression of **CD80 or CD86** and **CD40** are among the properties which **distinguish** specialized antigen presenting cells (termed **professional APC**) from other MHC positive cells.

Accessory co-stimulatory molecules:

- A number of other molecules on the surface of APC may serve some role in co-stimulation, although their full role or mechanism of action is not clear.

- These include **VCAM-1, ICAM-1** and **LFA-3** on APC and their respective ligands **VLA-4, LFA-1** and **CD2** on T cells.

APC molecules:

VCAM-1 (vascular cell adhesion molecule 1):

Promotes **adhesion** of lymphocytes, monocytes, eosinophils, and basophils.

ICAM-1 (inter-cellular adhesion molecule 1):

Also known as **CD54**. Its concentration **increases** greatly on cytokine stimulation.

LFA-3 (lymphocyte function-associated antigen-3):

Also known as **CD58**.

T cell molecules:

VLA-4 (very late antigen-4):

It is an **integrin dimer** composed of **CD49d (alpha)** and **CD29 (beta).** Binds with **VCAM-1.**

LFA-1 (lymphocyte function associated antigen-1):

Involved in recruitment of cells to site of infection. Binds to **ICAM-1.**

CD2:

A cell adhesion molecule. It binds with **LFA-3.**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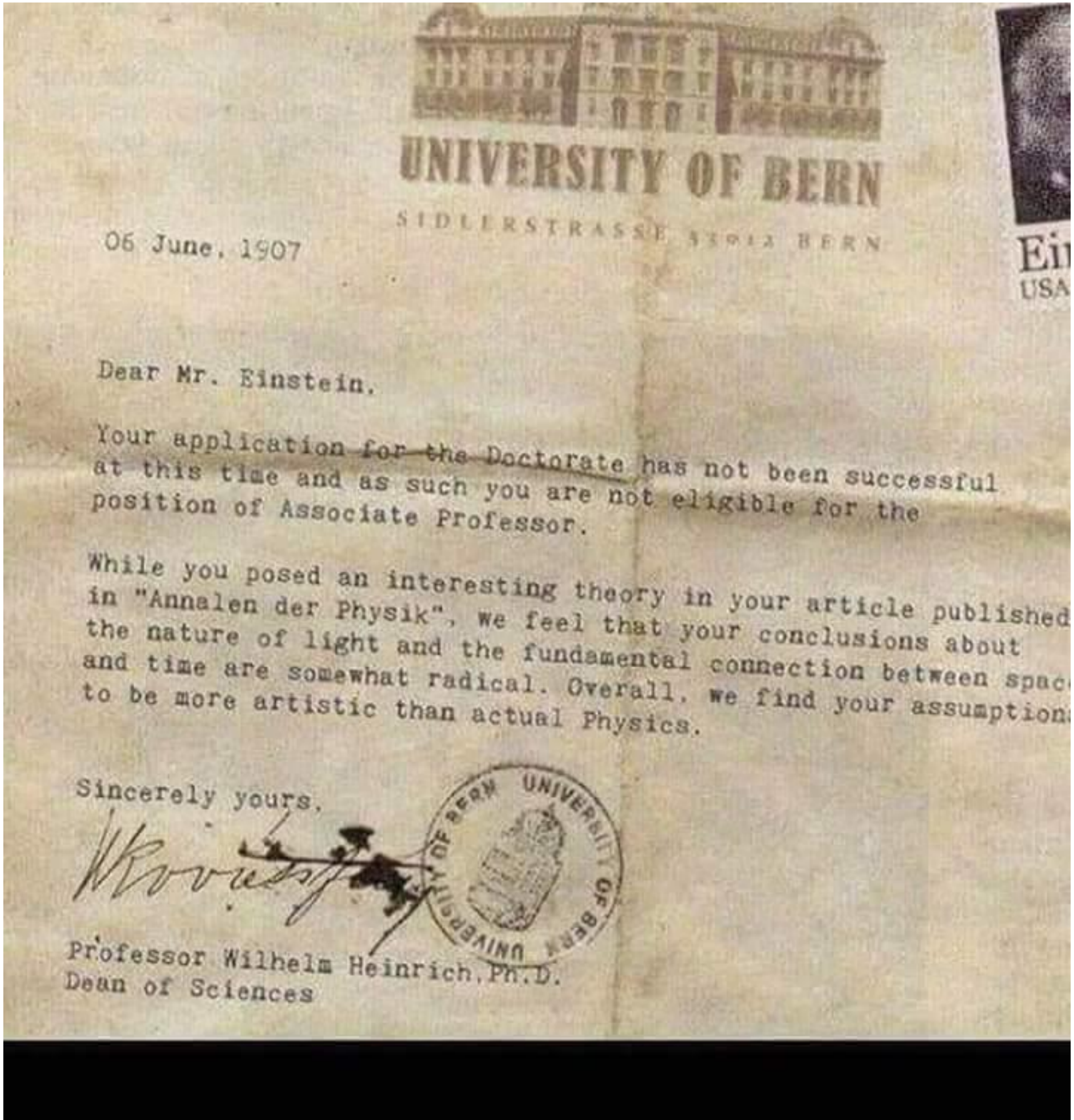

UNIVERSITY OF BERN

SIDLERSTRASSE 3012 BERN

06 June, 1907

Dear Mr. Einstein,

Your application ~~for the Doctorate~~ has not been successful at this time and as such you are not eligible for the position of Associate Professor.

While you posed an interesting theory in your article published in "Annalen der Physik", we feel that your conclusions about the nature of light and the fundamental connection between spac and time are somewhat radical. Overall, we find your assumption to be more artistic than actual Physics.

Sincerely yours,

Professor Wilhelm Heinrich, Ph.D.
Dean of Sciences

Paper was invented by Chinese in **2nd century BC** not for writing but for packaging and protection. It was used for writing many years later.


Thank You!